

AN OVER VIEW: MICROSPHERES AS A NASAL DRUG DELIVERY SYSTEM

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ABSTRACT

All types of microspheres that have been used as nasal drug delivery systems are water-insoluble but absorb water into the sphere's matrix, resulting in swelling of the spheres and the formation of a gel. The building materials in the microspheres have been starch, dextran, albumin and hyaluronic acid, and the bioavailability of several peptides and proteins has been improved in different animal models. Also, some low-molecular weight drugs have been successfully delivered in microsphere preparations. The residence time in the cavity is considerably increased for microspheres compared to solutions. However, this is not the only factor to increase the absorption of large hydrophilic drugs. The dextran microsphere system was as effective as an absorption enhancer for insulin as degradable starch microspheres (DSM). The mode of action for improved absorption found for starch microspheres is also applicable to dextran micro spheres. Microspheres also exert a direct effect on the mucosa, resulting in the opening of tight junctions between the epithelial cells.

Keywords: Nasal administration; microspheres; bioavailability; absorption enhancer; mucociliary clearance; mucosal toxicity.

INTRODUCTION¹:

Microspheres are solid spherical particles ranging in size from 1-1000 μ m. They are spherical free flowing particles consisting of proteins or synthetic polymers. The microspheres are free flowing powders consisting of proteins or synthetic polymers, which are biodegradable in nature. There are two types of microspheres; microcapsules and micromatrices, which are described as, Microcapsules are those in which entrapped substance is distinctly surrounded by distinct capsule wall and micromatrices in which entrapped substance is dispersing throughout the microspheres matrix. Solid biodegradable microspheres incorporating a drug dispersed or dissolved through particle matrix have the potential for the controlled release of drug. They are made up of polymeric, waxy, or other protective materials, that is, biodegradable synthetic polymers and modified natural products.

DIFFERENT TYPES OF METHODS FOR PREPARATION OF MICROSPHERES¹:

The microspheres can be prepared by using any of the several techniques given below but choice of the technique mainly depends on the nature of the polymer used, the drug, the intended use and the duration of therapy.

1) SINGLE EMULSION TECHNIQUE^{2, 3}:

The micro particulate carriers of natural polymers i.e., those of proteins and carbohydrates are prepared by single emulsion technique. The natural polymers are dissolved or dispersed in aqueous medium followed by dispersion in non-aqueous medium e.g., oil. In the second step of preparation cross-linking of the dispersed globule is carried out. The cross linking can be achieved either by

means of heat or by using the chemical crosslinkers. The chemical cross linking agent used include glutaraldehyde, formaldehyde, terephthaloyl chloride, diacid chloride, etc. Crosslinking by heat is carried out by adding the dispersion, to previously heated oil. Heat denaturation is however, not suitable for the thermolabile drugs while the chemical cross-linking suffers disadvantage of excessive exposure of active ingredient to chemicals if added at the time of preparation.

2) DOUBLE EMULSION TECHNIQUE^{3, 4}:

Involves the formation of the multiple emulsions or the double emulsion of type w/o/w and is best suited to the water-soluble drugs, peptides, proteins and the vaccines. This method can be used with both the natural as well as the synthetic polymers. The aqueous protein solution is dispersed in a lipophilic organic continuous phase. This protein solution may contain the active constituents. The continuous phase is generally consisted of the polymer solution that eventually encapsulates of the protein contained in dispersed aqueous phase. The primary emulsion is then subjected to the homogenization or the sonication before addition to the aqueous solution of the polyvinyl alcohol (PVA). This results in the formation of the double emulsion. The emulsion is then subjected to the solvent removal either by solvent evaporation or by solvent extraction process. The solvent evaporation is carried out by maintaining emulsion at reduced pressure or by stirring the emulsion so that the organic phase evaporates out. In the latter case, the emulsion is added to the large quantity of water (with or without surfactant) into which organic phase diffuses out. The solid microspheres are subsequently obtained by filtration and washing. A number of hydrophilic drugs like luteinizing hormone releasing hormone (LH-RH) agonist; vaccines,



proteins/peptides and conventional molecule are successfully incorporated in to the microspheres using the method of double emulsion solvent evaporation/extraction.

3) POLYMERIZATION TECHNIQUES^{3, 4}:

The polymerization techniques used for the preparation of the microspheres are mainly classified as:

- Normal polymerization
- Interfacial polymerization

Normal polymerization:

1) Bulk polymerization:

A monomer or a mixture of monomer along with the initiator is usually heated to initiate the polymerization and carry out the process. The catalyst or the initiator is added to the reaction mixture to facilitate or accelerate the rate of the reaction. The polymer so obtained may be molded or fragmented as microspheres. For loading of drug, adsorptive drug loading or adding drug during the process of polymerization may be adopted.

2) The suspension polymerization:

It is carried out by heating the monomer or mixture of monomers with active principles (drugs) as droplets dispersion in a continuous aqueous phase. The droplets may also contain an initiator and other additives.

3) The emulsion polymerization:

However, differs from the suspension polymerization as due to presence of the initiator in the aqueous phase, which later on diffuses to the surface of the micelles or the emulsion globules.

I. Interfacial polymerization⁵:

In Interfacial polymerization technique two reacting monomers are employed; one of which is dissolved in the continuous phase while the other being dispersed in the continuous phase. The continuous phase is generally aqueous in nature through which the second monomer is emulsified. The monomers present in either phase diffuse rapidly and polymerize rapidly at the interface. Two conditions arise depending upon the solubility of formed polymer in the emulsion droplet. If the polymer is soluble in the droplet it will lead to the formation of the monolithic type of the carrier on the hand if the polymer is insoluble in the monomer droplet, the formed carrier is of capsular (reservoir) type.

The degree of polymerization can be controlled by the reactivity of the monomer chosen, their concentration, and the composition of the vehicle of either phases and by the temperature of the system. Controlling the droplets or globules size of the dispersed phase can control the particle size. The polymerization reaction can be controlled by maintaining the concentration of the monomers, which can be achieved by addition of an excess of the continuous phase. The interfacial

polymerization is not widely used in the preparation of the microparticles because of certain drawbacks, which are associated with the process such as:

- Toxicity associated with the unreacted monomer
- High permeability of the film
- High degradation of the drug during the polymerization
- Fragility of microcapsules
- Non-biodegradability of the microparticles

4) PHASE SEPERATION AND COACERVATION:

Phase separation method is specially designed for preparing the reservoir type of the system, i.e. to encapsulate water soluble drugs e.g. peptides, proteins, however, some of the preparations are of matrix type particularly, when the drug is hydrophobic in nature e.g. steroids. In matrix type device, the drug or the protein is soluble in the polymer phase. The process is based on the principle of decreasing the solubility of the polymer in the organic phase to affect the formation of the polymer rich phase called the coacervates. The coacervation can be brought about by addition of the third component to the system which results in the formation of the two phases, one rich in the polymer, while the other one. In this technique, the polymer is first dissolved in a suitable solvent and then making its aqueous solution disperses drug. Phase separation is then accomplished by changing the solution conditions by using any of the method mentioned above. The process is carried out under continuous stirring to control the size of the microparticles. The process variables are very important since the rate of achieving the coacervate determines the distribution of the polymer film, the particle size and agglomeration of the formed particles. The agglomeration must be avoided by stirring the suspension using a suitable speed stirrer as the process of microsphere formation begins the polymerize globules start to stick and form the agglomerates. Thus the process variable critical as they control the kinetic of the formed particles since there is no defined state of equilibrium attainment.

5) SPRAY DRYING AND CONGEALING^{3, 4}:

Spray drying and spray congealing methods are based on the drying of the mist of the polymer and drug in the air. Depending upon the removal of the solvent or the cooling of the solution, the two processes are named spray drying and spray congealing respectively. The polymer is first dissolved in a suitable volatile organic solvent such as dichloromethane, acetone, etc. The drug in the solid form is then dispersed in the polymer solution under high-speed homogenization. This dispersion is then atomized in a stream of hot air. The atomization lead to the formation of small droplets or the fine mist from which the solvent evaporates leading to the formation of microspheres in a size range 1-100µm. Microparticles are separated from the hot air by means of the cyclone



separator while the traces of solvent are removed by vacuum drying.

6) SOLVENT EXTRACTION:

This method is used for the preparation of microparticles, involves the removal of the organic phase by extraction of the organic solvent. The method involves water miscible organic solvent such as isopropanol; organic phase is removed by extraction with water. The process decreases the hardening time for the microspheres. One variation of the process involves direct addition of the drug or protein to polymer organic solution. The rate of solvent removal by extraction method depends on the temperature of water, ratio of emulsion volume to the water and the solubility profile of the polymer.

7) QUASSI EMULSION SOLVENT DIFFUSION⁵:

A novel quasi-emulsion solvent diffusion method to prepare the controlled release microspheres of drugs with acrylic polymers has been reported in the literature. Microsponges can be prepared by a quasi-emulsion solvent diffusion method using an external phase containing distilled water and polyvinyl alcohol (PVA). The internal phase is consisting of drug, ethyl alcohol and polymer is added at an amount of 20% of the polymer in order to facilitate the plasticity. At first, the internal phase is prepared at 60°C and added to the external phase at room temperature. After emulsification, the mixture is continuously stirred for 2 hours. Then the mixture can be filtered to separate the microsponges. The product is then washed and dried by vacuum oven at 40°C for 24 hours. Example: - Ibuprofen.

MICROSPHERES AS NASAL DRUG DELIVERY SYSTEM:

All types of microspheres that have been used as nasal drug delivery systems are water-insoluble but absorb water into the sphere's matrix, resulting in swelling of the spheres and the formation of a gel. The building materials in the microspheres have been starch, dextran, albumin and hyaluronic acid, and the bioavailability of several peptides and proteins has been improved in different animal models. Also, some low-molecular weight drugs have been successfully delivered in microsphere preparations. The residence time in the cavity is considerably increased for microspheres compared to solutions. However, this is not the only factor to increase

the absorption of large hydrophilic drugs. Microspheres also exert a direct effect on the mucosa, resulting in the opening of tight junctions between the epithelial cells. The nasal route for systemic drug delivery has mainly been investigated with large hydrophilic peptides and proteins in mind, although other type of drugs has also been investigated. Different types of absorption enhancers have been used to avoid the problem of low absorption.

On the basis absorptions two type of the polymers used in microspheres

1. Mucoadhesive
2. Bioadhesive

Mucoadhesion, as the word suggests, refers to adhesion of matter to a mucus layer for an extended period of time⁶. A mucoadhesive agent is thus a substance that adheres to mucus. The term bioadhesion is less specific and can be used to denote adhesion to any biological surface⁶⁻⁷. The effect of water-insoluble, mucoadhesive powder mixtures on the absorption of insulin was first investigated by Nagai *et al.*⁸, who concluded that they had a positive effect on the nasal absorption in comparison with a solution and a water-soluble powder formulation. Many investigations have since shown positive results for nasal delivery by mucoadhesive microparticles, *i.e.*, micron-sized particles of drug and excipients, in comparison with liquid formulations or the pure drug [e.g. Table 1]. Several mucoadhesive polymers, for example degradable starch microspheres, cellulose, carbomer, alginate and the popular, cationic polymer chitosan, have been investigated.

"Bioadhesion" in simple terms can be described as the attachment of a synthetic or biological macromolecule to a biological tissue. An adhesive bond may form with epithelial cell layer, the continuous mucus layer or a combination of the two. The term "mucoadhesion" is used specifically when the bond involves mucous coating and an adhesive polymeric device. The use of dry-powder formulations containing bioadhesive polymers for nasal administration of peptides and proteins water-insoluble cellulose derivatives were mixed with insulin and the powder mixture was installed into the nasal cavity.

Table 1: Summary of studies into the effects of dry, mucoadhesive microsphere on the systemic absorption of drugs after nasal administration to human subjects.

Delivery system	Substance	Bioavailability (%)	Reference
Degradable starch microspheres	Metoclopramide	137%, relative to a plain nasal liquid spray.	Vivien <i>et al.</i> 1994 [11]
Microcrystalline Cellulose	Salmon calcitonin	10%	Makino <i>et al.</i> 1995a [12]
Microcrystalline Cellulose	Glucagon	165%, relative to pure powder	Teshima <i>et al.</i> 2002 [14]
Chitosan	Morphine	54.6%; 10.5% from a plain nasal liquid spray	Illum <i>et al.</i> 2002 [13]



The powder took up water, swelled and established a gel with a prolonged residence time in the nasal cavity as a consequence. Bioadhesive polymers have since then been reported to decrease the mucociliary transport rate *ex vivo* on frog palate¹⁵ and *in vivo* in rats¹⁶. Several other groups have used similar formulations for the nasal delivery of drugs such as interferon, beclomethasone, and oxy-metazoline. The polymers used in those studies were microcrystalline cellulose (Avicel), hydroxypropyl cellulose (HPC) and hydroxypropyl methylcellulose (HPMC).

Bioadhesive microspheres as another way of prolonging the residence time in the nasal cavity were introduced by Illum et al. in 1987¹⁷. Microspheres of albumin, starch and DEAE-(Di-ethyl amino ethyl) dextran absorbed water and formed a gel-like layer which was cleared slowly from the nasal cavity. Three hours after administration, 50% of the delivered amounts of albumin and starch microspheres and 60% of the DEAE-dextran microspheres were still present at the site of deposition. It was suggested that an increased contact time could increase the absorption efficiency of drugs.

PHYSIOLOGICAL ASPECTS:

The main functions of the nose are olfaction and the conditioning of inspired air. The physiology of the nose is well suited for these purposes; the nasal cavity contains turbinates comprising a surface area of 150-180 cm² but allowing only a narrow pathway for the inspired air (*Figure 1*). Inhaled particles larger than 10 µm are thus efficiently kept in the nose at the same time as the air is heated and moistened. Three types of mucosa cover the surface of the nasal cavity. The stratified squamous epithelium is found in close proximity to the nostrils and gradually transforms into a pseudo stratified columnar epithelium, which covers most of the nasal cavity. The olfactory epithelium is situated in the upper posterior part of the nasal cavity (*Figure 1*) and covers approximately 10 cm² of the human nasal cavity; in comparison, the olfactory mucosa in rodents constitutes about 50% of the nasal cavity³.

The pseudo stratified columnar epithelium of the respiratory nasal mucosa consists of a single layer of four

main cell types: ciliated and nonciliated columnar cells, basal cells and goblet cells (*Figure 1*). The cells are covered by microvilli. Many, especially those in the posterior half of the nasal cavity, also have approximately 2005µm long cilia¹⁹, whose synchronized movements enable mucociliary clearance of unwanted particles from the nose. The epithelial cells are covered by a layer of mucus, which is thought to consist of two distinct layers, each approximately 5 µm in depth.

The cilia move in the low viscosity layer and as they project into the upper gel layer they push the mucus back to the nasopharynx at a speed of 3-25 mm/min. The mucus, produced by the submucosal glands and goblet cells, is composed of >90% water, 0.5-5% mucins (mucous glycoproteins), 1-2% salts and 0.5-1% free proteins²⁰. The mucosa is slightly acidic (pH 5.5-6.5), which is thought to be important for its antibacterial properties. The epithelial cells are secured in the basement membrane, a layer of collagen fibrils. The submucosa, which is highly vascularised and thus plays an important role in the systemic absorption of drugs, is situated under the basement membrane. The passive absorption of large hydrophilic molecules is likely achieved paracellularly, as opposed to more lipophilic molecules which may diffuse through the cells. Paracellular absorption is limited by the tight junctions connecting the epithelial cells on the apical side (*Figure 1*). The nasal mucosa is relatively permeable to drug molecules; the extent of absorption is lower than that from the lung but in the same order as that from the small intestine. Absorption has been shown to decrease significantly with size for hydrophilic molecules weighing more than 300 Da and is in general restricted for molecules weighing more than 1000 Da^{21, 22}. Absorption across the nasal mucosa can be further restricted by enzymatic degradation. The metabolic capacity is considered to be rather high²², especially in the olfactory mucosa^{22, 23}. It may be of consequence for the delivery of peptides and proteins, but fast absorption and high local concentration of the compound will decrease the risk of metabolism²².

Figure 1: The approximate place of the olfactory epithelium (Olf), the superior turbinate (ST), middle turbinate (MT) and inferior turbinate (IT) and to the right a ciliated columnar cell (CC), basal cell (BC), goblet cell (GC), nonciliated columnar cell (NC), tight junctions (TJ) and mucus layer (ML). A comparison can be made with the frontal section of the porcine snout

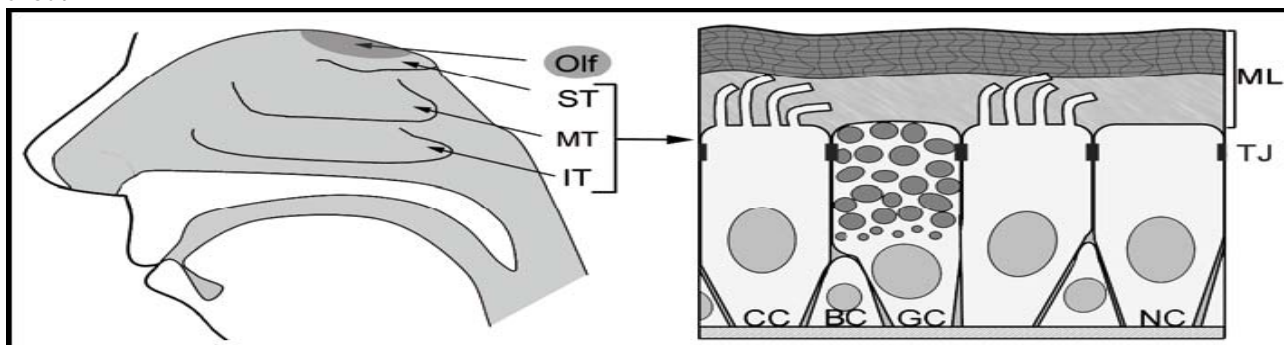


Figure 2: Possible routes of transport between the nasal cavity and the brain and CSF.

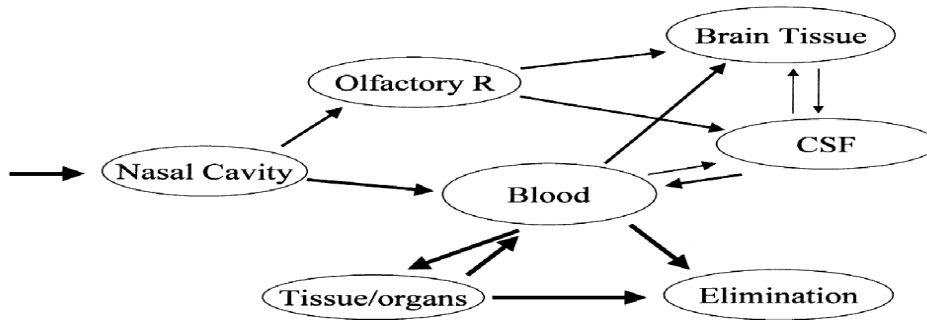


Figure 3: TEM picture of an open tight junction between Caco-2 cells after exposure to DSM³⁰.

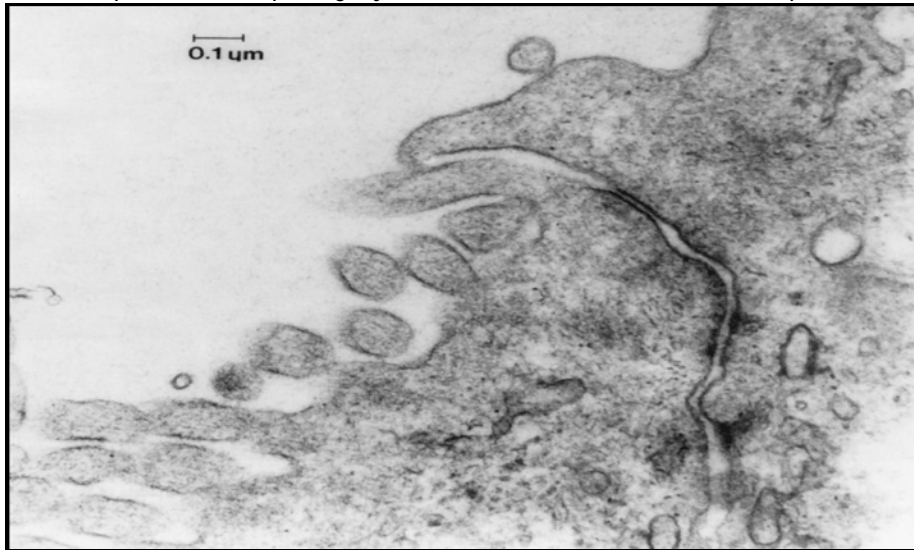
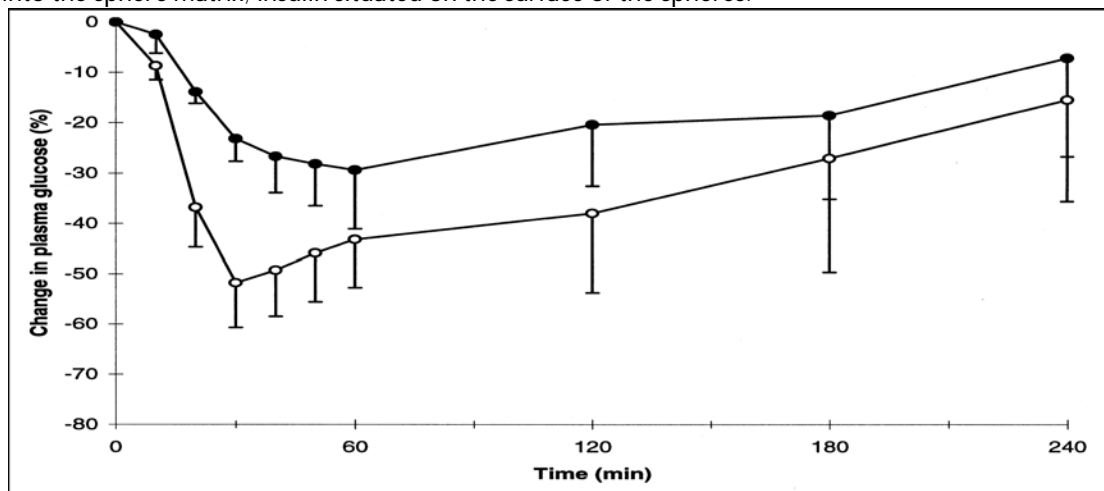


Figure 4: Changes in plasma glucose after intranasal administration of 1 IU/kg insulin in dextran microspheres to rats. Insulin incorporated into the sphere matrix; insulin situated on the surface of the spheres.



CHARACTERISTICS OF MICROSPHERES:

The most frequently used microsphere system for nasal drug delivery is degradable starch microspheres (DSM), also known as Spherex. These microspheres are prepared by an emulsion polymerization technique where starch is cross-linked with epi-chlorohydrine²³. Most drugs of interest are incorporated into the sphere matrix due to the high exclusion limit, i.e. molecules with a molecular weight less than 30000 Da can be incorporated

into the swollen microsphere matrix, whereas larger molecules are totally excluded from the microspheres. The particle size of the microspheres used in nasal drug delivery studies is about 45 mm in the swollen state.

A microsphere system based on dextran cross linked with epichlorohydrine has also been used for nasal drug delivery. These microspheres are commercially available under the brand names Sephadex and DEAE-Sephadex. In the latter, the glucose units in dextran are substituted

with diethyl aminoethyl groups, i.e. anion-exchange resins. The microspheres are available in particle sizes from 10 to 300 nm, although in nasal drug delivery only spheres less than 180 nm have been used. The degree of cross-linking differs between different grades. There is an inverse relationship between the degree of cross-linking and the degree of swelling. Consequently, the volume of liquid that the microspheres can hold in a swollen state is lower for spheres with a high degree of cross-linking than for spheres with a low degree of cross-linking. The exclusion limit ranges from 700 to 600000 Da for different grades of dextran microspheres.

For both the starch and the dextran systems, the drugs are loaded to the microspheres by a lyophilisation process²⁴. A water solution of the drug is added to the microspheres, which takes up the fluid and a gel is formed. The gel is then freeze-dried and the resulting powder is passed through a sieve to yield a homogeneous dry formulation.

Two different processes for the preparation of albumin microspheres have been described—a spray drying technique with an aqueous solution of nicotinic dipine and albumin²⁵ and an emulsification technique in which albumin propranolol microspheres were prepared²⁶. The particle sizes in the swollen state were about 10 and 40 nm, respectively. Spray-drying and emulsification are also used for preparing polyacrylic acid microspheres. The particles sizes obtained were in the range 1–10 nm in the dried state. Hyaluronic acid ester microspheres with a particle size of 6–8 nm were the result of an emulsification technique described by Illum et al.^[29]

MECHANISMS FOR IMPROVED DRUG ABSORPTION BY MICROSPHERES:

Although the residence time in the cavity is considerably increased for microspheres that absorb water in contact with the mucosa and form a gel, it seems that this is not the only factor in the increased absorption of large hydrophilic drugs. The mechanism for the increased absorption of drugs administered with degradable starch microspheres (DSM) has been shown to be due to an effect on tight junctions between the epithelial cells [30]. Mono layers of Caco-2 cells were investigated in a transmission electron microscope prior to, immediately after, 15 min after and 180 min after the administration of dry microspheres. It was clearly shown that the tight junctions started to separate after only 3 min and that the separation continued for up to 15 min after administration (Fig. 3). Thus, when the microspheres absorb water from the mucus and swell, the epithelial cells are dehydrated and cause the tight junctions to separate. After 3 h, the tight junctions between the Caco-2 cells were comparable with the controls, indicating that the enhancing effect of DSM is rapid and reversible. Since the process is reversible, an increase in absorption for drugs that are transported via the paracellular pathway will take place mainly during the short period when the tight junctions are separated. These findings are in

agreement with the rapid absorption of insulin and the normalization of glucose levels seen in animals when insulin was administered with DSM. For an optimum effect, the drug has to be available for absorption, i.e. dissolved, when the spheres swell by taking water from the mucus layer and the underlying epithelial cells, resulting in the temporary widening of the tight junctions. Additional evidence for the validity of this suggested mechanism of action is that the absorption-enhancing effect of DSM is lost when the microspheres are administered in a pre-swollen state³². Another hypothesis for the mechanism of absorption enhancement of dry powders was recently put forward by Oechslein et al. The authors suggest that it is the calcium-binding capacity of the powder formulation which determines the absorption of the somatostatin analogue octreotide. Among the powder formulations that were investigated, dextran microspheres (Sephadex) were also included in the study.

The peptide was mixed with the dry spheres, not loaded by lyophilisation as earlier described. The investigators found a correlation between the calcium-binding properties of the delivery system and the bioavailability of octreotide in rats. The Calcium-binding capacity for dextran microspheres was initially quite low, although pre swollen microspheres showed the highest calcium-binding capacity of the tested materials. Administration with these dextran microspheres resulted in the highest bioavailability for the test drug. It took 1 hr to reach peak plasma concentration in-vivo and the need for swelling before a good calcium-binding capacity was achieved was taken to be an explanation for this delay.

However, this mechanism cannot explain the results obtained for the same type of microspheres in an absorption study in rats by Pereswetoff-Morath and Edman. Insulin administered with dextran microspheres induced a maximum decrease in plasma glucose after 30–40 min. These findings are comparable to those published for insulin in degradable starch microspheres in rats. In the latter study, the plasma peak concentration of insulin was reached about 10 min after administration, which would most likely also be the case for the dextran microspheres due to the similar plasma glucose concentration profile. If calcium binding had been crucial for the insulin absorption from dextran microspheres in this study, it would not have been possible to reach the peak concentration so soon after administration. Oechslein estimated the pre-soaking time needed to achieve calcium binding to be at least 30 min, and this would result in a much later plasma concentration peak for insulin in the study by Pereswetoff-Morath and Edman.

IMPROVED NASAL DRUG ABSORPTION BY MICROSPHERES:

Microspheres of different materials have been evaluated in-vivo as nasal drug delivery systems. Degradable starch microspheres (DSM) increase the absorption of insulin,



gentamicin, human growth hormone, metoclopramide and desmopressin. Dextran microspheres have been used in-vivo as a delivery system for insulin and octreotide and have also been evaluated in vitro as a potential delivery system for nasally administered nicotine. Hyaluronic acid ester microspheres increase the absorption of insulin²⁹ and albumin microspheres have been used to deliver propranolol²⁸. Polyacrylic acid microspheres^{27, 28} and polyvinyl alcohol microspheres have as yet only been evaluated in vitro as potential nasal drug delivery systems. Although microspheres of different materials appear to act in a similar manner, there are also differences.

1. Dextran Microspheres¹⁷

The slowest clearance was detected for DEAE-dextran, where 60% of the delivered dose was still present at the deposition site after 3 h. However, these microspheres were not successful in promoting insulin absorption in rats. The insulin was too strongly bound to the DEAE groups to be released by a solution with an ionic strength corresponding to physiological conditions. In the same study, the dextran microspheres without the ion-exchange group induced a 25% decrease in plasma glucose about 40 min after the administration of insulin 1IU/ kg. The decrease in plasma glucose varied greatly between animals, probably due to the large size range of the microspheres (50–180 nm).

In a later study, the same insulin dose was administered with microspheres of a particle size 45 nm. When the insulin was situated on the surface of the microspheres, a 52% decrease in plasma glucose was induced 30 min after administration to rats. However, when microspheres which included insulin in the sphere matrix were used, the maximum plasma glucose decrease was 30%, reached after 60 min (Fig. 4). Thus, dextran microspheres with insulin on the surface of the sphere were more effective in promoting insulin absorption than spheres with insulin distributed into the sphere matrix. It is possible that the limited amount of fluid in the nasal cavity is responsible for the differences observed.

The microspheres have to be completely swollen to release all of the incorporated insulin. The limited amount of fluid in the nasal cavity will result in incomplete swelling. Thus, the release rate from microspheres with insulin incorporated into the sphere matrix will be more affected than for microspheres with insulin on the surface. Structural changes due to the lyophilisation process were observed in spheres with insulin incorporated, which probably further decreased the release rate. It was therefore concluded that the localization of insulin is of great importance to the in-vivo behavior of dextran microspheres. This conclusion is not valid as a general rule for microspheres, since the absorption-enhancing effect of DSM with the insulin incorporated into the microsphere matrix is as good as for the dextran microspheres with insulin on the surface.

Table 2: Nasal drug delivery in degradable starch microspheres (DSM)

Species	Drug	Addition enhancer	Dose	(min)	Absolute Bioavailability (%)	Relative Bioavailability (%)	Ref.
Rat	Insulin	---	75 IU/kg	8	30		[18]
		---	70 IU/kg	7	33		
Sheep	Insulin	---	2 IU/kg	12	4.5	10.7	[22]
		LPC	2 IU/kg	22	13.1	31.5	
Sheep	Gentamicin	---	5 mg/kg	24	9.7		[19]
		LPC	5 mg/kg	8	57.3		
Sheep	hGH	---	2.5 mg/kg	120		2.7	[22]
		LPC	2.5 mg/kg	60		14.4	

2. Degradable starch microspheres (DSM)

DSM is the most frequently used microsphere system for nasal drug delivery and has been shown to improve the absorption of insulin, gentamicin, human growth hormone, metoclopramide and desmopressin. The bioavailabilities are summarized in Table 2.

Insulin administered in DSM to rats resulted in a peak plasma concentration after 7–10 min (Fig. 5) and a rapid dose-dependent decrease in blood glucose. The maximum reduction in blood glucose level after doses of 0.75 and 1.7 IU/kg were 40 and 64%, respectively, and the absolute bioavailability was approx 30%.

The maximum decrease was reached about 40 min after administration, irrespective of the dose given. In line with

these results, a latter study by the same group³¹ showed that an insulin dose of 1 IU/kg gave a 45–50% reduction in plasma glucose, 30–40 min after administration.

DSM as a delivery system for insulin (2 IU/kg) has also been tested in sheep. The absolute bioavailability was 4.5% and the time to reach maximum effect, i.e. a 50% decrease in plasma glucose, was 60 min³³. The effect could be further improved by incorporating the absorption enhancer lysophosphatidylcholine (LPC) into the microspheres together with insulin. The plasma glucose profile was similar, with a maximum glucose decrease of 60%, but the bioavailability was improved to 13%.

The DSM system has also been used for other drugs. Gentamicin, a polar antibiotic compound, showed no too



little absorption from the nasal cavity when administered as a plain solution to sheep.

When administered in DSM, the peak plasma concentration was reached 24 min after dosing and was maintained for up to 60 min. The absolute bioavailability was 10% and, as with insulin, the bioavailability could be further improved by incorporating LPC into the spheres. In this case the bioavailability increased to 57% and the absorption was more rapid, with a plasma concentration peak after 8 min.

In the same animal model a similar trend was observed for biosynthetic human growth hormone (hGH) and desmopressin. However, the effect was not as pronounced as for gentamicin. The relative bioavailability of hGH was 3% when delivered in DSM and 14% when LPC was included. The plasma concentration peak was reached at 120min post-dosing when DSM was used and 60 min when also LPC was incorporated into the spheres. This delay of the plasma concentration peak was attributed to the low solubility of hGH, which was probably increased when LPC was included and hence the peak was reached sooner. Desmopressin was rapidly absorbed, with a *t* of 8 min for plain max DSM and 18 min for DSM with LPC. The absolute bioavailabilities for desmopressin were 5 and 10%, respectively.

Biodegradable starch microspheres have also been used in a clinical investigation of the nasal delivery of the antiemetic drug metoclopramide. The bioavailability was 137% compared to a nasal spray. A mixture of metoclopramide and microcrystalline cellulose administered as a dry powder did not result in increased absorption compared to the solution.

3. OTHER TYPES OF MICROSPHERES

The group in Nottingham has also used hyaluronic acid ester microspheres to deliver insulin to sheep²⁹. The relative bioavailability of 2 IU/kg insulin was the same as for the plain DSM, i.e. about 11%. However, the maximum decrease in plasma glucose of about 40–60% was reached after 90 min for the hyaluronic acid ester microspheres, compared to 60 min for the DSM.

Albumin microspheres containing propranolol with extended drug release resulted in a prolonged plasma concentration plateau in dogs²⁶. These microspheres were not administered as a dry-powder formulation, but in a suspension. About 50% of the incorporated propranolol was released in-vitro within 4 h. The maximum plasma concentration was obtained after 90 min, and an effective plasma concentration was maintained for up to 12 h. The absolute bioavailability was approx. 84%.

PHARMACEUTICAL APPLICATIONS:

The nasal cavity offers a large, highly vascularised subepithelial layer for efficient absorption. Also, blood is drained directly from nose into the systemic circulation, thereby avoiding first pass effect. However, nasal delivery

of drugs has certain limitations due to the mucociliary clearance of therapeutic agents from the site of deposition resulting in a short residence time for absorption. Use of BDDS increases the residence time of formulations in nasal cavity thereby improving absorption of drugs. It has been shown (Illum et al., 1987) by gamma scintigraphy study that radiolabelled microspheres made from diethyl amino ethyl dextran (DEAE-dextran), starch and albumins are cleared significantly more slowly than solutions after nasal administration in human volunteers. Hence, it was suggested by Illum et al. that the intranasal application of bioadhesive microspheres (in powder form) causes them to swell on coming in contact with the nasal mucosa to form a gel and decrease their rate of clearance from the nasal cavity, thereby providing poorly absorbed drugs a longer time for absorption.

1. The excellent absorption enhancing properties of bioadhesive microspheres are now being used extensively for both low molecular weight as well as macromolecular drugs like proteins. Nasal cavity as a site for systemic drug delivery has been investigated extensively and many nasal formulations have already reached commercial status including leutinising hormone releasing hormone (LHRH) and calcitonin (Illum, 1999).

2. Chitosan and starch are the two most widely employed bioadhesive polymers for nasal drug delivery. It has been reported that the clearance half-life was 25% greater for chitosan microspheres than for starch microspheres. This may be due to the differences in the surface charge, molecular contact and flexibility of two polymers. Chitosan exerts a transient inhibitory effect on mucociliary clearance of the bioadhesive formulations.

3. Other bioadhesive microspheres used for nasal administration of peptides and proteins include the cross-linked dextran microspheres, which are water insoluble and water absorbable. Sephadex and DEAE-Sephadex were found to improve the nasal absorption of insulin, but to a lesser extent than the starch microspheres (Edman et al., 1992). Hyaluronic acid ester microspheres were used for the nasal delivery of insulin in sheep and the increase in nasal absorption was found to be independent of the dose of microspheres in the range of 0.5–2.0 mg/kg (Illum et al., 1994).

ADVANTAGES:

1. A highly vascularised sub-epithelial layer allowing for rapid and direct absorption into the systemic circulation, avoiding first-pass hepatic metabolism.
2. A less hostile environment than the gastro-intestinal tract, resulting in reduces drug denaturing.
3. Improved patient compliance and comfort compared with intravenous administration.
4. Rapid absorption, higher bioavailability.
5. Avoidance of liver first pass metabolism



6. Avoidance of irritation of the gastrointestinal membrane. Reduced risk of overdose.
7. Non-invasive, therefore, reduced risk of infection.
8. Ease of convenience and self-medication. Reduced risk of infectious disease transmission.

LIMITATIONS:

The nasal route of delivery is not applicable to all drugs. In spite of high permeability of the nasal mucosa, many drugs may not be sufficiently absorbed. Lack of adequate aqueous solubility is often a problem. Note that the entire dose is to be given in a volume of 25–200 ml which

requires quite high aqueous drug solubility. Some drugs can cause nasal irritation. Others may undergo metabolic degradation in the nasal cavity.

The nasal route is less suitable for chronically administered drugs. For example, insulin for the treatment of type I diabetes may not be an appropriate drug candidate for nasal delivery because patients will need to administer this drug daily for the remainder of their lives. If a chronic drug is to be administered much less frequently, its nasal delivery may still be a viable option.

Table 3: List of prescription nasal products currently on the market

S.no	Product	Drug	Indication	Manufacturer
1	Beconase AQ Nasal Spray	Beclomethasone dipropionate monohydrate	Symptomatic treatment of seasonal and perennial allergic rhinitis	Allen and Hanbury's /GlaxoWellcome Inc.
2	Flonase Nasal Spray	Fluticasone propionate	Management of seasonal and perennial rhinitis	Allen and Hanbury's /GlaxoWellcome Inc.
3	VicksO SinexO Long Acting Decongestant Nasal Spray and Ultra Fine Mist	Oxymetazoline hydrochloride	temporary relief of nasal congestion associated with colds, hay fever and sinusitis	Proctor and Gamble

CONCLUSION

All types of microspheres that have been used as nasal drug delivery systems are water-insoluble but absorb water into the sphere's matrix, resulting in swelling of the spheres. The dextran microsphere system was as effective as an absorption enhancer for insulin as degradable starch microspheres (DSM). The maximum decrease in plasma glucose and the kinetics of the effect curve were similar for both systems. These systems also have a similar effect on mucosal integrity and lack a of adjuvant effect on the immune system after repeated nasal administration. It is therefore likely that the mode of action for improved absorption found for starch microspheres is also applicable to dextran micro spheres, i.e. separation of the tight junctions during the swelling process of the microspheres. An important factor for the absorption of large hydrophilic molecules is probably the initial availability of the drug during the period when the tight junctions are separated. The formulation of all kinds of microspheres as nasal drug delivery systems for peptides and proteins ought to take into account studies of the time for complete swelling of the spheres and the release rate of the incorporated drug under conditions resembling the situation in the nasal cavity. This is probably not as crucial for low-molecular weight drugs, which are absorbed to a larger extent without absorption enhancers and for which it is easier to achieve prolonged absorption by retaining the formulation in the nasal cavity for a longer period of time. The use of different types of microspheres as nasal drug delivery systems has been investigated mostly in rats and sheep, although dogs have

also been used. In these animal models the absorption of peptides and proteins has been successfully improved.

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